

REMARKS

In the Advisory of November 14, 2006, the Examiner states:

“The Examiner has provided a *prima facie* case stating that if the person of ordinary skill in the art would crystallize the KMD-3212 generated by Yamagishi et al or Kitazawa et al with the addition of the guidance supplied by Williamson, that the person of ordinary skill in the art would generate the claimed invention. Since no data was provided to show the results of modifying the references as set forth by the Examiner, the Declaration is not found to be persuasive to withdraw the rejection.”

Applicants further respond by submitting herewith an EXAMINATION REPORT by Mr. Kobayashi attached to the DECLARATION...1.132 of Mr. Tsuru. Applicants also provide the following discussion.

As a result of carrying out the Yamagishi et al procedure with the guidance of Williamson, submitted is an EXAMINATION REPORT by Mr. Kobayashi attached to the DECLARATION...1.132 of Mr. Tsuru (Tsuru Declaration).

As can be seen from the EXAMINATION REPORT and the Tsuru Declaration, even if the person of ordinary skill in the art were to refer to Yamagishi et al together with Williamson, that person would not generate the present  $\alpha$ -form crystal of KMD-3213. In case of the recrystallization of crude crystals of KMD-3213 of Yamagishi et al by using ethyl acetate as a recrystallizing solvent, impurities of Yamagishi et al may most affect crystallization of polymorphs. Thus, regardless of the degree of the temperature at the beginning of crystallization one will obtain  $\beta$ -form crystals of KMD-3213.

It is well known that polymorphism is often affected by the trace amounts of impurities. (Masaki Okamoto et al., Journal of Chemical Engineering of Japan, Vol. 37, No. 10, pp. 1224-

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1231, 2004; ATTACHMENT 2 of the Tsuru Declaration). In the case of the recrystallization of crude crystals of KMD-3213 per Yamagishi et al, trace amounts of impurities affects/ignore the polymorphism as taught in Okamoto et al.

Furthermore, as stated in the Declaration of Mr. Tsuru, Yamagishi et al prepared KMD-3213 as a synthetic intermediate for producing the indole compound disclosed in Example 1. Thus, the KMD-3213 of Yamagishi et al was not a subject compound of the Yamagishi et al invention. Accordingly, one of ordinary skill in the art would not have been motivated to attempt to modify the Yamagishi et al procedure by the guidance of Williamson to generate the present  $\alpha$ -form crystal of KMD-3213.

Additionally, the present  $\alpha$ -form crystal of KMD-3213 is the most preferable of the crystal forms for an oral solid medicament with respect to stability and hygroscopicity (lines 16-19 on page 6 of the present specification); the present invention is related to such findings. Neither of Kitazawa et al nor Yamagishi et al disclose or suggest said superiority of the present  $\alpha$ -form crystals of KMD-3213.

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The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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